NBN 99) of rat neublastin exhibit biological activity as measured by their ability to induce RET autophosphorylation.

The Examiner requested that applicants submit publications confirming that the experimental systems used in the application to demonstrate neublastin biological activity are accepted in the art. The following publications confirm that assays similar to those described in the present application have been used to characterize the biological activity of other members of the GDNF ligand subfamily.

The enclosed publication of Kotzbauer et al. (1996) Nature 384:467-70 establishes the neurotrophic activity of neurturin and GDNF by demonstrating their ability to support the survival of sympathetic neurons and sensory neurons of the nodose and dorsal root ganglia (page 469). As noted above, the experimental results contained in the present application confirm the neurotrophic activity of neublastin by demonstrating its ability to promote survival of dopaminergic neurons and dorsal root ganglion cells (Examples 6-8).

The enclosed publication of Lindahl et al. (2001) J. Biol. Chem. 276:9344-51 describes the characterization of the neurotrophic factor persephin. For example, Lindahl et al. measures RET autophosphorylation in cells treated with persephin as a means to assess persephin-induced bioactivity (pages 9347 and 9350). These experiments are analogous to the neublastin-induced RET autophosphorylation assays described in the present application (Examples 11 and 12). In addition, Lindahl et al. assesses the ability of persephin to promote survival of neurons expressing RET and GFRα4. Similarly, the present application demonstrates the ability of neublastin to promote neuronal survival (Examples 6-8).

The publications of Kotzbauer et al. and Lindahl et al. confirm that it is accepted in the art to measure the ability of a protein to promote survival of neurons as a means of assessing the protein's neurotrophic activity. In addition, the publications confirm that induction of RET autophosphorylation is used in the art as a means of assessing bioactivity of the members of the GDNF ligand subfamily, all of which signal through the RET receptor tyrosine kinase.

Relationship Between Rat and Human Neublastin Truncates

The Examiner asked for clarification as to the relatedness of the human and rat neublastin truncates NBN 104, NBN 102, and NBN 99. Human pre-pro neublastin corresponds to SEQ ID NO:9 and rat pre-pro neublastin corresponds to SEQ ID NO:34. As detailed in the following alignments, the human and rat truncates are identical at 92.3 % (NBN 104), 93.1% (NBN 102), and 93.9% (NBN 99) of their amino acid residues.

NBN 104 (92.3% identity)

```
Human           AAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLASLLGAGALRP 60
Rat             ATDARGCRLRSQLVPVSALGLGHSSDELIRFRFCSGSCRRARSPHDLSLASLLGAGALRS 60
                *:.************* ****** ****:*******************************.

Human           PPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 104
Rat             PPGSRPISQPCCRPTRYEAVSFMDVNSTWRTVDHLSATACGCLG 104
                ******:***************************:**********
```

NBN 102 (93.1% identity)

```
Human           GARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLASLLGAGALRPPP 60
Rat             DARGCRLRSQLVPVSALGLGHSSDELIRFRFCSGSCRRARSPHDLSLASLLGAGALRSPP 60
                .************* ****** ****:*******************************.**

Human           GSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 102
Rat             GSRPISQPCCRPTRYEAVSFMDVNSTWRTVDHLSATACGCLG 102
                ****:***************************:**********
```

NBN 99 (93.9% identity)

```
Human           GCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLASLLGAGALRPPPGSR 60
Rat             GCRLRSQLVPVSALGLGHSSDELIRFRFCSGSCRRARSPHDLSLASLLGAGALRSPPGSR 60
                *********** ****** ****:*******************************.*****

Human           PVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 99
Rat             PISQPCCRPTRYEAVSFMDVNSTWRTVDHLSATACGCLG 99
                *:**************************:**********
```

In view of the specification's demonstration of bioactivity for the rat truncates NBN104, NBN102, and NBN99 (Examples 11 and 12) and the high relatedness between the rat and human proteins, the person of ordinary skill in the art would understand that that corresponding human truncates form a ternary complex with RET and GFRα3, trigger RET autophosphorylation, and induce neurotrophic activity. The neurotrophic activity of the claimed polypeptides (and

pharmaceutical compositions containing same) constitutes a specific, substantial, and credible utility.

Conclusions

Applicants respectfully submit that all claims are in condition for allowance, which action is requested.

Please apply any charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13751-056001.

Respectfully submitted,

Date: July 5, 2006

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